UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,335	04/08/2004	Simon C. Robson	01948/095002	8550

21559 7590 01/18/2007

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
SCHLAPKOHL, WALTER	
ART UNIT	PAPER NUMBER
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/820,335	ROBSON ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *4-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 April 2004 and 26 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/19/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the papers filed 12/11/2006. Claims 1-22 are pending. Claims 4-22 are withdrawn. Claims 1-3 are under examination in the instant Office action.

Election/Restrictions

Applicant's election without traverse of Group II (claims 1-3) in the reply filed on 12/11/2006 is acknowledged.

Claims 4-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/11/2006.

The restriction is still deemed proper and is therefore made FINAL.

Specification

The disclosure is objected to because of the following informalities: on page 27, line 21, the disclosure makes reference to Figures 4A and 4B; however, no such figures exist in the application. It appears Applicant intended to reference Figures 9A and 9B.

Appropriate correction is required.

Claim Objections

Claims 1 and 3 are objected to because of the following informalities: claim 1 recites "[a] method of diagnosing a mammal having or at risk of having an autoimmune condition, wherein said a reduction in NTPDase biological activity identifies said mammal as having or at risk of having said condition" in lines 1-3 (emphasis added). Claim 1 should instead recite "[a] method of diagnosing a mammal having or at risk of having an autoimmune condition, wherein ~~said~~ a reduction in NTPDase biological activity identifies said mammal as having or at risk of having said condition."

Claim 3 is objected to because the claim comprises non-elected subject matter.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods for diagnosing a mammal having or at risk of having an autoimmune condition, wherein a reduction in NTPDase biological activity identifies said mammal as having or at risk of having said condition. The claims encompass any mammal, any NTPDase sequence or biological activity and any autoimmune condition. Claim 2 is limited to such methods wherein the autoimmune condition is Addison's disease, alopecia, ankylosing spondylitis, antiphospholipid syndrome, Bechcet's disease, chronic fatigue syndrome, Chrohn's disease, ulcerative colitis, diabetes, fibromyalgia, Goodpasture syndrome, Graves' disease, idiopathic thrombocytopenic purpura, lupus, Meniere's multiple sclerosis, myasthenia gravis, pemphigus vulgaris, primary biliary cirrhosis, psoriasis, rheumatoid arthritis, rheumatic fever, sarcoidosis, scleroderma, vasculitis, vitiligo or Wegener's granulomatosis. Claim 3 is

limited to such methods wherein the reduction in NTPDase activity is a reduction in the level of NTPDase protein. The claims do not provide any structural information with regard to the NTPDase sequences capable of being used such that an autoimmune condition in a mammal can be diagnosed or such that a mammal's risk of having an autoimmune condition can be diagnosed. The claims do not provide any information with regard to which biological activities are capable of use such that an autoimmune condition in a mammal can be diagnosed or such that a mammal's risk of having an autoimmune condition can be diagnosed. Thus, the rejected claims comprise a set of proteins/protein sequences and biological activities that are defined by the function of the encoded protein, i.e. it's ability to allow for diagnosis or risk of any autoimmune condition.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification lists examples of NTPDases, including CD39, CD39L1-L4, potato

apyrase, hepatic canilicular ecto-apyrase, Golgi-associated ecto-ATPase, ecto-uridine diphosphatase (UDPase), lysosomal ecto-apyrase, LAP70 and alpha-sarcoglycan (page 4, lines 1-4). The specification describes colonic tissue from an unspecified number of patients which revealed increased CD39 protein and mRNA levels in both Crohn's disease and ulcerative colitis tissue samples (see Example 1, pages 25-26 and Figure 1). The specification provides a general teaching that diagnostic assays to predict or diagnose a mammal as having or at risk for an autoimmune disorder can be performed (page 21, lines 9-25). The specification teaches such assays are based on the discovery that NTPDases such as CD39 can suppress the autoimmune and inflammatory responses in autoimmune disorders by its ability to modulate nucleotide-sensitive P2 receptors on inflammatory cells (ibid). No description is provided of a single NTPDase amino acid sequence which can be used to predict a single autoimmune disorder, much less ANY autoimmune disorder. No description is provided of the use of a any biological activity of an NTPDase such that the biological activity was used to diagnose a mammal as having or at risk of having an autoimmune disorder.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only

representative of one protein capable of being used to diagnose a mammal as having or at risk of having Crohn's disase or ulcerative colitis. The results are not necessarily predictive of any other NTPDases capable of being used in such a diagnosis. The results are not predictive of the any other autoimmune disorder outside of Crohn's disease or ulcerative colitis. Thus it is impossible to extrapolate from the example described herein those NTPDase molecules that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of NTPDase genes or proteins that can be used to diagnose a mammal as having or at risk of having any autoimmune disorder. Ford et al (US Patent No. 6,335,013) teach that decreased levels of CD39-L2 or CD39-L4 polypeptides may be used to diagnose or prognose one or more types of cancer, but Ford et al do not explicitly teach the use of an NTPDase to diagnose an autoimmune disease (see entire document, especially column 24, lines 5-67; and column 36, lines 12-24).

Given the very large genus of amino acid molecules encompassed by the rejected claims, as well as the large genus of biological activities of such molecules and the large genus of potential autoimmune disorders which can be diagnosed by

detection of reduced activity of such molecules; and given the limited description provided by the prior art and specification with regard to the sequences capable of fulfilling the claim limitations of claims 1-3, the skilled artisan would not have been able to describe the broadly claimed genus of NTPDase protein sequences/biological activities that can be used to diagnose a mammal as having or at risk of having any autoimmune condition. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those protein acid sequences and/or those NTPDase activities that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded Applicant was not in possession of the claimed invention for claims 1-3.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of

the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art, the amount of experimentation necessary and the relative skill levels of those in the art. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: The claims are drawn to methods for diagnosing a mammal having or at risk of having an autoimmune condition, wherein a reduction in NTPDase biological activity identifies said mammal as having or at risk of having said condition. The claims encompass any mammal, any NTPDase sequence, any NTPDase biological activity and any autoimmune condition. Claim 2 is limited to such methods wherein the autoimmune condition is Addison's disease, alopecia, ankylosing spondylitis, antiphospholipid syndrome, Bechcet's disease, chronic fatigue syndrome, Chrohn's disease, ulcerative colitis, diabetes, fibromyalgia, Goodpasture syndrome, Graves' disease, idiopathic thrombocytopenic purpura, lupus, Meniere's multiple sclerosis, myasthenia gravis, pemphigus vulgaris, primary biliary cirrhosis, psoriasis, rheumatoid arthritis, rheumatic fever, sarcoidosis, scleroderma, vasculitis, vitiligo or Wegener's granulomatosis. Claim 3 is limited to such methods wherein the reduction in NTPDase activity is a reduction in the

level of NTPDase protein. The invention is complex in that it involves measuring a change in any biological activity of any NTPDase protein, such that a reduction in activity or protein level is indicative of a mammal which has or is at risk of having any autoimmune disorder. At a minimum, the nature of the invention requires knowledge of a correlation between the expression of polypeptide with NTPDase biological activity and the presence of or predisposition to an autoimmune condition.

Breadth of the claims: The claims are extremely broad in that they encompass diagnosing a mammal having ANY autoimmune condition or simply at risk of having ANY autoimmune condition by detecting a decrease in ANY NTPDase biological activity of any NTPDase. Applicant has defined an "NTPDase" as "any polypeptide that exhibits an activity common to its related, naturally occurring NTADase" (page 6, lines 27-28). Furthermore, the specification teaches that a biological activity of an NTPDase includes hydrolysis of nucleotide triphosphates into nucleotide diphosphates and inorganic phosphate or into nucleotide monophosphates and pyrophosphate (see, e.g., page 7, lines 3-19). NTPDase biological activity can also include decreases in autoimmune responses below untreated control levels as measured by standard techniques (ibid) and changes in NTPDase mRNA or protein levels (see, e.g.,

claim 3). The large breadth of the claims exacerbates the complexity of the invention.

Guidance of the specification/The existence of working examples: The specification lists examples of NTPDases, including CD39, CD39L1-L4, potato apyrase, hepatic canilicular ecto-apyrase, Golgi-associated ecto-ATPase, ecto-uridine diphosphatase (UDPase), lysosomal ecto-apyrase, LAP70 and alpha-sarcoglycan (page 4, lines 1-4). The specification describes colonic tissue from an unspecified number of patients with Crohn's disease and/or ulcerative colitis which revealed increased CD39 protein and mRNA levels (see Example 1, pages 25-26 and Figure 1). The specification provides a general teaching that diagnostic assays to predict or diagnose a mammal as having or at risk for having an autoimmune disorder can be performed (page 21, lines 9-25). The specification teaches that such assays are based on the discovery that NTPDases such as CD39 can suppress the autoimmune and inflammatory responses in autoimmune disorders by its ability to modulate nucleotide-sensitive P2 receptors on inflammatory cells (ibid).

The specification fails to provide any guidance with regard to the NTPDase polypeptides which can be used for diagnosing a patient having an autoimmune condition vs. NTPDase polypeptides

used for diagnosing mammals at risk of having an autoimmune disorder.

The specification does not teach how much lower the level of expression of such any NTPDase protein or how much lower any biological activity of such a protein in a test autoimmune-diseased tissue/patient sample relative to the corresponding expression level or biological activity of said protein in a normal autoimmune-diseased tissue/patient sample must be in order for a diagnosis to be reached.

The specification does not provide any statistical analysis of the expression level of an NTPDase in different autoimmune-diseased vs. normal samples.

The specification does not differentiate or teach how to differentiate the use of differences in protein expression level or NTPDase biological activity in order to diagnose the presence of an autoimmune condition vs. the presence of inflammatory response to foreign antigens/pathogens.

State of the prior art: The literature reports examples of NTPDase polypeptides in methods for the prevention and treatment of inflammation and the use of NTPDase inhibitors in the treatment of hyperactive immune disorders. For example, Kumamoto et al (US Patent No. 7,067,254) teach the provision to a subject of a polypeptide encoding an NTPDase for preventing

and/or treating autoimmune diseases and/or allergies (see, e.g., column 27, lines 46-57 and column 28, lines 1-11). Mizumoto et al teach that the NTPDase CD39 modulates Langerhans cell-associated ecto-NTPDase activity and that CD39 deficiency in skin inflammation and immune responsiveness leads to opposing outcomes (*Nature Medicine* **8**(3):358-365, 2002; IDS Ref.; see entire document, especially the Abstract; page 361, Figure 4; and page 362, Figure 5). Ford et al (US Patent No. 6,335,013; cited above) teach that decreased levels of CD39-L2 or CD39-L4 polypeptides may be used to diagnose or prognose one or more types of cancer (see entire document, especially column 24, lines 5-67; and column 36, lines 12-24). However, the literature does not explicitly report the use of an NTPDase biological activity to diagnose a mammal as having or at risk of having an autoimmune condition. Thus, the state of the art is underdeveloped with respect to the use of any NTPDase biological activity, including the use of NTPDase protein levels in methods to diagnose autoimmune disorders, including Crohn's disease and ulcerative colitis.

Predictability of the art/Amount of experimentation necessary: The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art by Wu (*J. Pathol.* **195**(1):53-65, 2001.). Wu teaches that gene expression data must

be interpreted in the context of other biological knowledge, involving various types of "post genomics" informatics, including gene networks, gene pathways, and gene ontologies (page 53, left column). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (page 63 - Discussion). Additionally, post-filing art reveals that most gene association studies are typically wrong. Lucentini (*The Scientist*, page 20, Dec. 20, 2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revised statistical methods should be included in the gene association studies (middle column, 1st full paragraph).

Such unpredictability is exacerbated by the fact that NTPDases are present in extremely low amounts, making their isolation and definitive identification very difficult until recently as taught by Kumamato et al (cited above, see column 13, liens 50-52).

Given the complex nature of invention and the underdeveloped state of the art at the time of filing, there would be a large and prohibitive amount of experimentation required to make and use the claimed invention. Even for claims specifically reciting CD39 protein expression levels and a particular autoimmune condition, one would have to establish a statistically significant reduction in CD39 protein expression in a patient with the disease and a patient without the disease such that the difference were indicative of the autoimmune disease at the exclusion of other inflammatory conditions. This would include analysis of the different levels of expression in a large number of individuals first to establish what level of gene expression is considered "elevated" relative to a "normal" level of expression. One would then have to establish that elevated protein expression is correlated with the presence of a given autoimmune condition and perform studies that prove a correlation with the protein expression and a predisposition to the presence of or the development of the disease in the future.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 are rejected under 35 U.S.C. 102(e) as being anticipated by Ford et al (US Patent No. 6,335,013).

Ford et al teach the detection of reduced levels of the NTPDase CD39L2 and CD39L4 in a patient (see entire document, especially column 24, lines 5-67; and column 36, lines 12-24). Although Ford et al explicitly teach that the detection of a reduction in the level of CD39L2 and/or CD39L4 protein levels may be indicative of cancer, such a teaching meets the claim limitations of claims 1-3 because the detection of such a decrease would also (inherently) be indicative of a mammal having or at risk of having an autoimmune disorder.

Conclusion

No claim is allowed.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of

such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at (800) 786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Thursday from 8:30 AM to 6:00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

January 2, 2007

NANCY VOGEL
PRIMARY EXAMINER